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December 19, 2005

VIA HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Comments Regarding Docket No. 2005P-0420

Dear Sir or Madam:

On behalf of our client, Barr Laboratories, Inc., we submit the attached comments in response to the October 12, 2005 citizen petition filed on behalf of Shire Pharmaceuticals Group, plc, regarding generic versions of the brand-name drug Adderall XR. For the reasons set forth in Barr's comments, and the accompanying statement of Statement of Marvin C. Meyer, Ph.D., the Agency should immediately deny Shire's meritless petition.

As required by 21 C.F.R. § 10.30, we include an original and 4 copies of these comments.

Should you have any questions regarding these comments, please do not hesitate to contact me. Barr appreciates the opportunity to respond to this petition, and requests its prompt denial so that all eligible ANDAs can be finally approved without delay.

Very truly yours,

RAKOCZY MOLINO MAZZOCHI SIWIK LLP

Christine J. Siwik

CJS/af
Enclosures 2005P-0420

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Comments of Barr Laboratories, Inc.
Regarding Docket No. 2005P-0420

INTRODUCTION

The goal of Shire's petition, like so many innovator petitions, is clear: preservation of its brand-name drug monopoly. In this instance, a monopoly on the drug Adderall XR – a product that generated more than $881 million in sales for Shire during the 12-month period ending July 2005, according to IMS Health data.

Barr filed the first ANDA seeking FDA approval to market generic Adderall XR products and challenging the patents that Shire has had the Agency list in connection with NDA No. 21-303. Shire turned around and used these patents to trigger two 30-month stays of Barr's ANDA approval. With the last of the stays set to expire in just a few months, Shire apparently has decided to expand its anticompetitive generic-blocking strategy, hoping to use the citizen petition process to delay Barr's final approval beyond expiration of the last 30-month stay. Shire's petition, however, fails to raise any scientifically-supported basis for FDA to discard the Agency's long-standing and well-established bioequivalence (or "BE") criteria when approving ANDAs for Adderall XR.

Briefly, Shire bases its citizen petition on an absurd premise. FDA gave Shire the opportunity to avoid performing the clinical trials that NDA applicants typically must conduct to demonstrate the safety and efficacy of a new drug product. Specifically, FDA said that Shire could avoid carrying out clinical trials on its then-new extended release Adderall formulation if Shire could demonstrate "superimposable" pharmacokinetic ("PK") data comparisons between the unapproved extended-release formulation and two separately-administered doses of Shire's previously-approved immediate release Adderall formulation. Absent superimposability, FDA said that Shire would have to do a clinical trial. From this, Shire asks the Agency to leap to the unwarranted and scientifically-invalid conclusion that an ANDA applicant must demonstrate superimposability between the PK data for its generic Adderall XR formulation and the PK data for Adderall XR itself. While the Agency apparently would have accepted superimposable PK data, in lieu of standard clinical trials, when approving Shire's Adderall XR product, Shire offers no legitimate reason why FDA should jettison its standard BE criteria when it comes to comparing generic extended release products with an already-approved extended release reference listed drug, such as Adderall XR. Shire's petition should be denied.

Significantly, FDA should deny Shire's petition immediately, as it merely raises arguments that the Agency already rejected when denying Ferring's citizen petition relating to desmopressin. (*See* FDA 7/1/05 Admin. Ruling in 2004P-0068/CP1 ("FDA Desmopressin Ruling"), Ex. A hereto). In that petition, Ferring, like Shire here, attempted to delay generic competition by arguing that ANDA applicants should be required to establish bioequivalence using tests other than traditional PK studies; conduct studies on children; and conduct clinical trials. FDA correctly rejected all of these arguments. (*Id.*). Unfortunately, final approval of Barr's desmopressin ANDA nevertheless appears to have been delayed in the process. While the court granted Barr's motion for summary judgment in Ferring's patent infringement case on February 7, 2005, FDA did not finally approve Barr's ANDA until July 1, 2005 – the day that it

denied Ferring's petition. The same should not happen here. The final 30-month stay of approval of Barr's Adderall XR ANDA expires on or about February 18, 2006. FDA should not allow Shire's groundless petition to hold up final approval of Barr's ANDA.

In sum, Shire's demand for "a more stringent bioequivalence requirement" for Adderall XR ANDAs is about delaying generic market entry and not about good science. Indeed, Shire's petition is so bereft of merit that the Agency should immediately deny this petition, and under no circumstances allow it to delay final approval of any otherwise eligible ANDA. Any other result would be profoundly anti-consumer, with the Agency rewarding Shire's misconduct with an unjustified extension Shire's of monopoly over this product.

DISCUSSION

Shire's petition seeks to impose clinically unnecessary requirements on ANDA applicants in an effort to delay the entry of generic competitors into the market. Specifically, Shire asks FDA to require all ANDA applicants to demonstrate "superimposability" of plasma concentration profiles; perform additional partial area under the curve ("AUC") measurements; and conduct studies in children. (Shire Pet. at 2). For any ANDA applicant that cannot satisfy its demands, Shire asks FDA to force such an applicant to conduct full clinical studies. (*Id.*). Shire's petition is absurd, challenging the very foundation of the ANDA approval process. Indeed, in this important respect, Shire's petition is strikingly similar to Ferring's desmopressin citizen petition. Like Ferring, Shire asks FDA to depart from the generally preferred methodology for determining bioequivalence for an oral dosage form product. (FDA Desmopressin Ruling at 2). And like Ferring, Shire provides the Agency with no scientifically-supported basis for seeking such a drastic departure. FDA should reach the same conclusion here that it reached in desmopressin:

> [T]he reliability and the relative merits of methodologies to assess BE are well established. Essentially, you request that, in the case of [Adderall XR], the Agency augment and modify the generally preferred methodology for determining BE for oral dosage form products. However, you offer no convincing evidence (i.e., data or other information) that any of your proposed changes are needed. Accordingly, not having been presented with any basis for departing from our long-established and well-settled practice, we deny your petition in its entirety.

(*Id.* (footnote omitted)).

As discussed below, and in the attached Statement of Marvin C. Meyer, Ph.D., Shire's citizen petition has no scientific merit. Shire provides no scientific evidence that would justify anything beyond conventional PK studies to establish BE of generic products. Indeed,

Shire does not raise any science-based concern that even suggests that FDA should require additional studies beyond the PK studies ordinarily sufficient to establish BE for generic ANDA drug products. Because Shire presents no scientifically-supported reason to expect that a BE study conducted using a properly validated analytical method will not provide acceptable evidence of the bioequivalence of a generic and innovator dosage form of extended-release mixed amphetamine salts products ("MASP"), its petition should be denied, and should be denied immediately. (Meyer Stmt., Ex. B hereto).

I. Now That Shire Has Established The Safety And Efficacy Of Adderall XR, ANDA Applicants Can Use Conventional PK Studies To Establish Bioequivalence And Obtain Agency Approval.

Now that Shire has established the safety and efficacy of Adderall XR, ANDA applicants can use conventional PK studies to establish bioequivalence or obtain approval. Shire's arguments to the contrary (Shire Pet. at 2-8) lack any scientific support. Nothing about Adderall XR renders a conventional PK study inadequate to establish BE to the reference listed drug ("RLD"). (Meyer Stmt. at 2-5).

A. FDA Should Reject Shire's Unsupported Demand That ANDAs Referencing Adderall XR Demonstrate "Superimposability" Or Carry Out Clinical Trials.

Shire asks FDA to require an ANDA applicant either to show identical plasma concentration profiles between its generic Adderall XR formulation and the branded Adderall XR product itself or to conduct clinical trials. (Shire Pet. at 2-4). According to Shire, ANDA applicants must demonstrate superimposability or conduct a clinical because these are the options that FDA provided Shire before approving Adderall XR. (*Id.*). Nonsense. FDA required such data from Shire in order to determine whether Adderall XR was safe and effective. Now that Shire has provided the required data, ANDA applicants can use conventional PK studies to establish BE. Under the relevant statutory and regulatory scheme, ANDA applicants do *not* have to repeat the same time-consuming safety and efficacy studies that the brand company performed. Indeed, Congress expressly did away with such a requirement with the 1984 Hatch-Waxman Amendments. Shire's petition, therefore, asks the Agency to turn back the clock more than two decades and ignore the entire ANDA approval process as it exists today. FDA should deny Shire's petition without delay, particularly given that Shire offers no scientific evidence to support the extraordinary relief sought.

At the time that Shire sought approval for Adderall XR, only the immediate-release (or "IR") formulation had been tested clinically. No clinical evidence existed to establish that the extended-release (or "XR") formulation would be safe and effective, and no clinical evidence existed to assess how sensitive the clinical effect would be to differences between the

IR and XR formulations in their respective blood concentration profiles. In short, no reference formulation existed and thus it could not be predicted how any significant deviation from the plasma concentration-time profile for the IR formulation might affect safety or efficacy. And based upon the *possibility* that "the rate of input *may* be related to clinical efficacy," FDA expressed concern over a "slightly different kinetic pattern between the IR and ER Adderall® formulations." (Shire Pet., Ex. C (emphasis added); *see also* Meyer Stmt. at 2-3).

Against this backdrop, FDA offered Shire a choice as to how Shire could prove the safety and efficacy of its then-unapproved XR formulation of Adderall – provide data to show a "superimposable" plasma concentration between Shire's IR and XR formulations (because no clinical evidence existed to demonstrate the safety and efficacy of an XR formulation) or conduct sufficient clinical trials. Shire had to select the latter because it could not demonstrate superimposable plasma concentrations between its IR and XR formulations. Shire's petition, therefore, misrepresents FDA's statements and inappropriately applies FDA's concerns regarding an XR dosage form that had never been studied in a clinical trial, to a BE study conducted for an ANDA that a references an XR dosage form that has been studied clinically and approved as safe and efficacious. (Meyer Stmt. at 3).

Now that Shire has established safety and efficacy, the Agency can follow its long-standing and well-established practice of requiring conventional PK studies to establish BE. Nothing more is required. Under that practice, any generic product that meets FDA's BE criteria for C_{max} and AUC parameters should also provide acceptable safety and efficacy. (Meyer Stmt. at 2-3). Indeed, this concept underlies the entire ANDA approval process, as FDA explained when denying Ferring's desmopressin citizen petition:

> [Hatch-Waxman] created section 505(j) of the Act, which describes the current approval process for ANDAs and the central rule of BE testing in it. ***The showing that must be made for an ANDA to be approved is different from that which is required in a new drug application (NDA).*** An NDA must show that the drug is safe and effective, generally through data and information derived from clinical and pre-clinical trials. In contrast, if an ANDA applicant can demonstrate that its generic drug product is the same as the RLD in certain respects (e.g., active ingredient, dosage form, route of administration), and is bioequivalent to the RLD, the statute permits an ANDA to rely on FDA's previous finding that the RLD is safe and effective.

(FDA Desmopressin Ruling at 2-3 (footnotes omitted and emphasis added)). Thus, an ANDA applicant need not demonstrate that the plasma profile concentrations of its generic formulation are superimposable upon the plasma profile concentrations of Adderall XR, or otherwise conduct

clinical trials. With Shire's available data, ANDA applicants can use traditional PK studies to demonstrate BE to Shire's branded products. (Meyer Stmt. at 2-3).

Finally, Shire claims that FDA required plasma concentration profiles for Adderall XR to be identical to those resulting from twice-daily IR administration because: (1) symptoms of ADHD are experienced throughout the course of a day; (2) the rate of absorption of the extended release formulation impact its clinical efficacy; and (3) different technologies for extended drug release, and varying amounts of amphetamine salts, may result in a product that is not equivalent to Adderall XR. (Shire Pet. at 4). Even if true, such claims have no relevance here. The fact that FDA required Shire to prove identical plasma concentration profile or to conduct a clinical study does not mean that FDA should impose such a requirement on ANDA applicants now that the Agency has Shire's data for the reasons discussed above. But FDA can, in fact, reject Shire's arguments on these specific points for the following additional reasons.

First, Shire's claim that "clinical effectiveness at particular time periods is clinically important" because symptoms of ADHD occur over the course of a day does not support a "superimposability" requirement. (Shire Pet. at 4). As an initial matter, this vague statement, even if true, is applicable to a great variety drugs and yet FDA does not require *all* ANDA applicants to prove clinical effectiveness through superimposability. (Meyer Stmt. at 3). More importantly, Shire offers no scientific evidence as to why clinical effectiveness must be proven over the course of the day for generic formulations of extended-release of MASP now that Shire has established the clinical effectiveness of Adderall XR through clinical studies. (*Id.*). Absent such evidence, Shire offers FDA no reason to take the extraordinary step of imposing a superimposability requirement on ANDA applicants. (*See, e.g.*, FDA Desmopressin Ruling (declining to deviate from standard PK studies to establish BE where the petitioner failed to provide a scientifically-supported reason for doing so)).

Second, when arguing that "the rate of input (absorption) of an extended-release drug indicated for management of ADHD symptoms impacts clinical efficacy" (Shire Pet. at 4), Shire primarily relies upon a study "A Randomized, Double-Blind, Placebo- and Active-Controlled, Crossover Study of SLI 381 in Children with Attention Deficit Hyperactivity Disorder." (Shire Pet., Ex. D). Shire's reliance on this study is misguided. (Meyer Stmt. at 3). The data in the Adderall XR study is not directed towards the need for a particular input rate, but instead shows that absorption must be sufficiently rapid to result in a therapeutic concentration, and this absorption must be continued long enough for an appropriate duration of activity. (*Id.*). Regarding the PK/PD relationship, this study "observed a *moderate* relationship between plasma drug levels and pharmacodynamic measures for amphetamine." (Shire Pet., Ex. D at 68) (emphasis added). This statement does not provide persuasive scientific evidence for the importance of absorption rate, and certainly does not counsel in favor of requiring ANDA applicants to meet Shire's "superimposability" requirement. (Meyer Stmt. at 3).

Third, Shire's statement that technologies for extended drug release, and varying amounts of amphetamine salts, may result in a product that is not equivalent to Adderall XR, also is an unremarkable statement. (Shire Pet. at 4). Again, even if true, this factor does nothing more than highlight importance of requiring that generic formulations be bioequivalent to the RLD drug. (Meyer Stmt. at 3). As discussed above, superimposability is not necessary to establish bioequivalence, which can be accomplished using conventional PK studies. (*Id.* at 2-4).

B. Partial AUC Measurements Are Not An Appropriate Means Of Establishing Bioequivalence.

Shire asks FDA to require ANDA applicants to make additional AUC assessments. (*See* Shire Pet. at 2, 6-8). For the reasons discussed above, such additional testing is unnecessary now that Shire's clinical studies have determined that Shire's XR formulation is safe and effective. Indeed, having proven this point, Shire itself went on to use conventional BE measures (C_{max} and AUC) to demonstrate that its proposed XR formulation also was safe and effective if the capsules were opened and the contents sprinkled on applesauce before consumption. (Meyer Stmt. at 4). Specifically, based upon the documents accompanying its petition, Shire concluded BE based on the conventional C_{max} and AUC parameters only, without calculating the additional early AUC parameters or requiring that such early AUC parameters meet the stringent BE criteria demanded in its current petition. (*See, e.g.*, Shire Pet., Ex. G; Meyer Stmt. at 4). In fact, Shire reached this conclusion even though its documents demonstrate that the blood concentration profile curves of the XR product under fasting conditions and those after consuming the product with applesauce did not meet the superimposability test that Shire is now demanding for ANDA applicants. (*Id.*).

Furthermore, Shire's request would require the Agency to depart from the generally preferred methodology for determining BE for oral dosage form products. Yet, Shire once again fails to provide the Agency with a scientifically-supported basis for seeking such a departure. And, of course, FDA's own guidance suggests that assessment of partial AUC only is necessary for immediate-release drugs, not controlled-release drugs. (*Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations* at 8 (Mar. 2003) ("BA/BE Guidance")). While Adderall XR may have an immediate-release component, it is a controlled-release drug. Thus, early AUC measurements are not necessary. (*See* Meyer Stmt. at 4).

Given this, it should not be surprising that Shire provides no evidence that the additional AUC measures it identifies should be required from ANDA applicants seeking to establish bioequivalence to the RLD. Consequently, FDA should reach the same conclusion here that it reached in denying Ferring's desmopressin petition: absent compelling scientific

evidence, the Agency will not impose additional requirements for ANDA approval at the brand company's request. (*See, e.g.*, FDA Desmopressin Ruling at 6 (refusing to require comparative clinical data given that Ferring "d[id] not provide any evidence that any of this additional data or information is needed to demonstrate BE")).

Finally, the Agency's BA/BE Guidance states that "[a]n early exposure measure may be *informative* on the basis of appropriate clinical efficacy/safety trials and/or pharmacokinetic/pharmacodynamic studies that call for better control of drug absorption into the systemic circulation." (BA/BE Guidance at 8 (emphasis added)). The Guidance in no way suggests that partial AUC measurements are sufficient or necessary to prove bioequivalence. (Meyer Stmt. at 4). And, here too, Shire fails to present any scientific evidence that a bioequivalence study using Adderall XR as a reference requires early exposure measurements.

II. Studies On Children Are Unnecessary.

In addition to asking FDA to force ANDA applicants to perform additional and clinically-unnecessary studies to establish bioequivalence, Shire requests that the Agency erect an additional roadblock to generic market entry – the testing of ANDA products on children. (Shire Pet. at 3, 8). Shire has no factual basis for making this request. Instead, Shire relies (yet again) on suggestion, speculation, and irrelevant observations. For this reason alone, FDA should deny Shire's request, just as it did Ferring's request for studies in children in connection with the drug desmopressin. (*See* FDA Desmopressin Ruling at 9, 12-13). And, in truth, the factual evidence that does exist – research conducted on Shire's behalf – supports the use of healthy adults to establish bioequivalence in all patient populations. This is, of course, consistent with Agency practice.

Absent Shire presenting data that demonstrates that a generic extended-release MASP product is bioequivalent to the PK parameters in adults, but nevertheless is not bioequivalent in children, there is no legitimate reason to require ANDA applicants to test their products in children. (Meyer Stmt. at 5). Shire, of course, offers no such data. Instead, Shire *suggests* that bioequivalence between children and adults *may* be different because the pharmacokinetics of Adderall XR in adults differ from that of children. (Shire Pet. at 8). Based upon its rank speculation, Shire argues that if an ANDA applicant is unable to show identical plasma concentration profiles in a bioequivalency study, then the applicant should be required to conduct efficacy clinical studies in children, adolescents, and adults. This argument, too, lacks merit.

First, it would be unethical to conduct PK studies in vulnerable populations such as children unless such studies were absolutely necessary. FDA specifically recommends that "unless otherwise indicated by a specific guidance, subjects recruited for in vivo BE studies be 18 years of age or older and capable of giving informed consent." (BA/BE Guidance at 7). *See*

also 63 Fed. Reg. 66632, 66640-41 (Dec. 2, 1998) ("FDA . . . does not currently require bioequivalence studies to be conducted in children for generic drugs."); 65 Fed. Reg. 19777, 19779 (Apr. 12, 2000) ("Bioequivalence comparisons of pediatric formulations with the adult oral formulation typically should be done in adults.").[1] And, of course, FDA's regulations articulate the principle of avoiding unnecessary human testing. (*See* FDA Desmopressin Ruling at 4).

Second, the Agency's regulations specifically provide for BE tests to be conducted in healthy adults absent a compelling reason to the contrary. As FDA explained in denying Ferring's request that ANDA applicants be required to conduct studies in children:

> [A]s our regulations specifically provide, BE studies should generally be conducted in normal (healthy) adults. Because several factors can influence a drug's BA, BE testing in healthy adults is preferred to control for as many non-drug related variables as possible. This approach is the most sensitive, as it best allows any differences in relative BA that are attributable to differences between drug formulations to be revealed.

(FDA Desmopressin Ruling at 12 (footnotes omitted)).

Third, the fact that the pharmacokinetics of Adderall XR differs in children and adults does not preclude the use of PK data from adults to establish bioequivalence. It is well known that the pharmacokinetics of a drug can differ in adults and children. (Meyer Stmt. at 5). This does not mean that bioequivalence of all drugs that are useful in children must be studied in both children and adults. In fact, it is unlikely that two products that are bioequivalent in adults will not be bioequivalent in children. (*Id.*). When filing an ANDA, generic manufacturers are not trying to extrapolate an appropriate children's dose. Rather, they are trying to establish bioequivalence between two different formulations using comparative studies. Comparative PK studies in adults are not only perfectly acceptable to prove bioequivalence, but also are the preferred means for establishing bioequivalence between two formulations. (*Id.*). Similarly, the fact that the pharmacokinetics of Adderall XR differs in children compared to adults is irrelevant to a bioequivalence study with a crossover design. (*Id.*). A number of drugs are indicated for use in children, but FDA does not require bioequivalence studies on those drugs to be conducted in children despite the differences in PK. (*Id.*).

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[1] While FDA recommends conducting PK studies in children in order to determine the appropriate dose level to use in clinical safety and efficacy studies (*see* Draft Guidance, *General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products*, at 4 (Nov. 1998)), nothing would warrant subjecting young children (some as young as six years old) to the discomfort of extensive blood sampling as part of an additional and unnecessary PK study, the sole value of which is to help Shire maintain its monopoly on extended-release MASP. (Meyer Stmt. at 5).

Fourth, the research and studies conducted on Shire's own behalf further undermine its current position that FDA should require studies in children. Based upon the exhibits submitted with its petition, a number of studies in Shire's NDA were based on or included healthy, normal adults. (Meyer Stmt. at 5). For example, Shire relied on a study of healthy adult subjects – 18 to 55 years of age – to establish the bioavailability of the RLD and to determine the effect of food. (*See* Shire Pet., Ex. G). Yet, Shire's package insert fails to make a distinction between adults and children with respect to the effect of food. (*See* Meyer Stmt. at 5).

In sum, the insincerity of Shire's arguments for requiring studies on adolescents and children is obvious. Not only does Shire fail to offer any data to support such a requirement, but studies conducted on its own behalf directly contradict its current position. FDA should not require extended-release MASP ANDA applicants to conduct studies on children to establish bioequivalence, just as FDA refused to do with respect to desmopressin:

> As you observe, DDAVP and other oral desmopressin products may behave differently in children than adults. However, you have articulated no scientifically substantiated reason – nor are we aware of any, based on available data concerning desmopressin and other drugs – why a generic oral desmopressin product shown to be bioequivalent to DDAVP in healthy adults would not be bioequivalent to the RLD in the approved pediatric population. Thus, your claim that a generic oral desmopressin product that is bioequivalent to DDAVP in adults may not be bioequivalent in children is unsupported.

(FDA Desmopressin Ruling at 13 (footnote omitted); *id.* at 9 (refusing to require tests in children, stating "you offer no evidence that BE in children cannot be inferred from BE testing in healthy adults, and we are aware of no such evidence")).

III. FDA Should Not Require Adderall XR ANDA Applicants To Conduct Clinical Trials To Demonstrate Safety And Efficacy.

Shire states that clinical trials should be required if an ANDA applicant's bioequivalence studies fail to show "identical plasmas concentration-time profiles." (Shire Pet. at 8). The reasons for refusing to require "identical" profiles for a generic product already has been discussed. The reasons for refusing to require clinical trials are equally as obvious and compelling.

FDA views clinical studies as far less reliable than PK studies to establish bioequivalence. *See* 21 C.F.R. § 320.24(b)(4). (*See also* Meyer Stmt. at 4). Indeed, the Agency's own regulations state that a clinical trial approach "is the *least accurate, sensitive and reproducible* of the general approaches for . . . demonstrating bioequivalence." 21 C.F.R.

§ 320.24(b)(4) (emphasis added). FDA has therefore concluded that only "[w]here there are no other means" should a clinical trial approach be used to provide evidence of bioequivalence. (BA/BE Guidance at 9-10). As discussed above, other, and more preferred, means for establishing bioequivalence do exist with respect to Adderall XR (*e.g.*, PK studies). (Meyer Stmt. at 4).

Even Shire does not appear to take its own suggestion seriously. Shire offers no data in support of a clinical studies requirement, nor any reason to adopt such a requirement. (Shire Pet. at 2-3, 8). Thus, Shire offers no reason for FDA to deviate from its long-standing policies and practices, under which FDA has concluded that clinical endpoint studies should only be used when no other testing options are available. (*See, e.g.*, BA/BE Guidance at 9-10; Meyer Stmt. at 4). As discussed above, a properly validated PK study would be sufficient to establish bioequivalence and thus clinical studies should not be used. (Meyer Stmt. at 2-4). FDA should not require ANDA applicants to conduct clinical trials under these circumstances. (*Id.* at 4). The Agency reached the same conclusion when denying Ferring's request for clinical studies with respect to desmopressin ANDAs:

> You [Ferring] do not provide any evidence that [comparative clinical data] is needed to demonstrate BE, however, or that conventional BE testing is not adequate to establish the BE of generic oral desmopressin products to the RLD; nor are we aware of any evidence to support your assertions. ***Therefore, we do not agree that the comparative clinical studies you request must be provided in ANDAs for generic oral desmopressin products.***

(FDA Desmopressin Ruling at 6 (emphasis added)).

CONCLUSION

Shire's citizen petition merely is an anticompetitive tactic designed to delay generic market entry for as long as possible. Shire's arguments have no basis in science, fact, the controlling statutory scheme, FDA regulations, or Agency practice. Indeed, Shire's arguments fly in the face of long-standing and well-established Agency precedent, making it incumbent on the Agency to act quickly when denying Shire's petition in its entirety. Any other result harms not only ANDA applicants, but the public that needs lower-priced generic drug products.

Respectfully submitted,

RAKOCZY MOLINO MAZZOCHI SIWIK LLP

Christine J. Siwik
On behalf of Barr Laboratories, Inc.